RESEARCH ARTICLE

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Doxorubicin Effects Breast Cancer Proliferation via the *NEAT1/miR-410-3p* Axis

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Abstract

Background: Doxorubicin (DOX) is an anthracycline derivative, a conversant chemotherapeutic agent, and one of the most influential chemotherapeutic drugs. Long noncoding RNAs (lncRNAs) play a vital role in this process. The current review demonstrates that lncRNAs can function as oncogenic and tumor suppressors and contribute to cancer development and progression. Our study addressed the nuclear-enriched abundant transcript 1 (*NEAT1*) and the effect of DOX on the regulation of *miR410-3p* by *NEAT1*. **Methods:** An MTT assay was conducted to determine the half-maximal inhibitory concentration. The initial step was RNA isolation, which was performed after the cell culture. Then, cDNA synthesis was carried out for both miRNAs and lncRNAs to use RT-PCR to identify changes in RNA expression. Alterations in expression levels were measured by quantitative real-time polymerase chain reaction analyses. This web-based analysis was performed using the Student's t-test. **Results:** After DOX treatment, *NEAT1* expression levels decreased in human breast cancer (BC) cells, including MDA-MB231 and MCF-7. As expected, further expression than in cancer cell lines was detected in the normal mammary epithelial cell line MCF-10A. Simultaneously, *miR410-3p* expression levels exhibited an increase in BC cells. Our data demonstrated that *NEAT1* expression was suppressed in cancer cells treated with doxorubicin, suggesting a potential therapeutic effect. **Conclusion:** These data indicate that DOX may affect BC lines via *NEAT1*, and that *miR410-3p* is effective in this pathway. Our data confirm the contribution of *NEAT1* and *miR410-3p* to DOX treatment. Therefore, they can be used as a biomarker for the diagnosis and treatment of BC.

Keywords: Doxorubicin- *NEAT1*- long non-coding RNA- Breast Neoplasms- miRNA410.

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Introduction

Breast cancer (BC) ranks first among all types of cancers in women worldwide and accounts for one-fourth of all cancers. According to the International Agency for Research on Cancer (IARC), female BC is the most prevalent cancer type and the fifth most common cause of cancer-related mortality [1, 2]. Traditional chemotherapy is an essential mainstay of cancer therapy. Chemotherapy is mainly aimed at killing cancer cells using chemotherapeutic chemicals. Doxorubicin (DOX), a powerful chemotherapeutic agent, is widely used for the treatment of BC [3–5]. The topoisomerase activity of DOX plays a vital role in its tumorigenicity inhibition. It can covalently bind to DNA replication and transcription proteins that interfere with the DNA helix [3, 6].

Non-coding RNAs (ncRNAs) are a growing heterogeneous group of genes that regulate most biological processes in human cells [7, 8]. In recent years, long ncRNA (lncRNAs), a class of endogenous RNAs, have been implicated in a wide range of disorders, cancers, and immune responses. LncRNAs lead to the progression of various cancers by acting as oncogenes or tumor suppressors [9, 10].

The nuclear-enriched abundant transcript 1 (*NEAT1*), a recently discovered vital element of nuclear paraspeckles, is dysregulated in various solid cancers [11]. Owing to its role in tumor initiation and progression, *NEAT1* dysregulation in cancer is related to metastasis, recurrence rate, and patient survival. Hence, it has been reported to be an oncogene in breast tumors, osteosarcomas, and endometrial carcinomas. There is a relationship between metastasis, tumor size in BC, and *NEAT1* overexpression [11–13]. It has been demonstrated that metastasis is decreased by inhibition of *NEAT1* expression. Only a limited body of research has evaluated *NEAT1* in BC, whereas other studies have addressed its hypoxia-induced impact on cellular proliferation [11]. The expression levels of miR-410-3p vary among different cancer types. Its impact on disease progression depends on the specific

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molecular targets it regulates in each type of cancer. Earlier research has shown that miR-410 acts as an oncogene in lung and colorectal cancers, whereas it functions as a tumor suppressor in breast and pancreatic cancers [14]. The purpose of this study is to examine the expression levels of lncRNA *NEAT1* and *miR410-3p* in MDA-MB231 and MCF-7 cell lines and their association with DOX, a frequently used drug in BC treatment.

Materials and Methods

Cell culture

MCF-7, MCF-10A, and MDA-MB-231 cells were obtained from Dr. Tokgün. MDA-MB-231 and MCF-7 cells were cultured in RPMI-1640 medium with 10% heat-inactivated fetal bovine serum and 1% penicillin/streptomycin (Capricorn Scientific, Ebsdorfergrund, Germany) in a 95% air/5% CO2 incubator at 37 °C. MCF-10A cells were cultured in DMEM/F12 medium with 5% heat-inactivated horse serum, 20 ng/ml EGF, 10 ug/ml insulin, 0.5 ug/ml hydrocortisone, and 1% penicillin/streptomycin (Gibco; Thermo Fisher Scientific, Inc.) in a 95% air/5% CO_2 incubator at 37 °C.

Cytotoxicity determination with MTT assay

The MTT assay was performed to determine the half-maximal inhibitory concentration (IC_{50}) of DOX (Cell Signaling Technology, Danvers, MA, USA). Cells were seeded at a density of 10,000 cells per well in 96-well plates containing medium supplemented. After 24 hours of incubation, cells were treated with serial dilutions of doxorubicin (0.1, 0.25, 0.5, 1, 2.5, 5, 7.5, and 10 μM) in triplicate for 24, 48, and 72 hours. At the indicated time points, 10 μL of MTT solution was added to each well and incubated for 4 hours at 37°C. The medium was then discarded, and formazan crystals were solubilized with 200 μL DMSO (Carlo Erba Reagent, Italy) per well. Absorbance was measured at 570 nm with a reference wavelength of 630 nm using a microplate reader. Cell viability was calculated relative to untreated controls, and IC_{50} values were determined accordingly.

Total RNA isolation

Total RNA was extracted using RNeasy MinElute spin columns (GeneAll Hybrid-RTM; Geneall, Seoul, Korea), according to the manufacturer's instructions. In summary, cultured cells were transferred to Eppendorf tubes. Chloroform was added and separated after five minutes at room temperature. The aqueous phase was collected by centrifugation, and the miRNAs were transferred to new Eppendorf tubes after a few steps.

cDNA synthesis

Real-time polymerase chain reaction (RT-PCR) was used to detect alterations in lncRNA and microRNA expression by reverse transcription, using commercial kits (A.B.T. Laboratory Industry, Turkey) was used for cDNA synthesis. Furthermore, cDNA synthesis was performed using a reverse transcription kit, and the reactions were carried out in 96-well plates with a real-time PCR device. Accordingly, the final concentration of RNA in the cDNA synthesis mixing procedure was adjusted to 2 μg.

To assess RNA expression levels, complementary DNA (cDNA) synthesis was performed for both lncRNA and microRNA using commercial reverse transcription kits (A.B.T. Laboratory Industry, Turkey). Total RNA (2 μg) was used as input in a 96-well plate format. The procedure was carried out according to the manufacturer's protocol. Briefly, the reaction mix was incubated at 25°C for 10 minutes, followed by 120 minutes at 37°C for reverse transcription, and finalized with 5 minutes at 85°C to inactivate the enzyme. Synthesized cDNAs were stored at −20°C until use in quantitative real-time PCR (qRT-PCR) for expression analysis.

Quantitative RT-PCR (RT-qPCR)

After reverse-transcription into cDNA, qPCR was conducted using SYBR Green mix (A.B.T. Turkey) on a Rotor-Gene Q PCR system (Qiagen, Germany). The primers used were *NEAT1* Forward: 5'- GTACGCGGGCAGATAACAC-3'- Reverse: 5'- TGCGTCTAGACACCACAACC-3'; *miR410-3p* forward: 5'-CCG CAC GAT ATA ACA CAG ATG-3'; reverse: 5'-GTG CAG GGT CCG AGG TAT TC-3.'

Quantitative real-time PCR (qRT-PCR) was performed using a 96-well plate format with a total volume of 10 μL per reaction, consisting of 5 μL SYBR Green Master Mix (A.B.T. Turkey), 2 μL nuclease-free water, 1 μL gene-specific primer, and 2 μL cDNA. Reactions were sealed with optical adhesive film and run in a real-time PCR system (Qiagen, Germany). The amplification conditions for *NEAT1* were initial denaturation at 95°C for 10 min, followed by 40 cycles of 95°C for 10 s, 62°C for 45 s, and 72°C for 30 s. For miR-410, the cycling protocol was 95°C for 15 min, followed by 45 cycles of 94°C for 15 s, 55°C for 30 s, and 70°C for 30 s.

GAPDH was used as the internal control for *NEAT1*, and U6 snRNA was used for miR-410 normalization. Relative expression levels were calculated using the $2^{-\Delta\Delta CT}$ method.

Potential Targets Analysis

Potential targets of Neat1 were identified using Encori (https://rnasysu.com/encori/). Subsequently, hierarchical classification and plot analysis of the identified potential targets were performed using ShinyGO (https://bioinformatics.sdstate.edu/go/). Additionally, the signalling pathways of potential targets were analyzed by PantherDB (https://pantherdb.org/).

Statistical analysis

GraphPad Prism 9 was used to generate linear graphs from the IC_{50} data. Expression alterations were determined using the $2^{-\Delta\Delta CT}$ method and web-based RT2 lncRNA PCR data analysis (Qiagen, Hilden, Germany). This web-based analysis was performed based on Student's t-tests.

All experiments were performed in triplicate, and data are presented as mean ± standard deviation (SD). A p-value of < 0.05 was considered statistically significant.

Results

NEAT1 downregulation in cancer cell lines treated with DOX

NEAT1 in two BC cell lines (MCF-7 and MDA-MB-231) and normal mammary epithelial cells (MCF-10A) was detected by RT-PCR after DOX treatment. Based on the PCR results, *NEAT1* levels were significantly downregulated in all human BC cells compared to those in MCF-10A cells. Compared to cells without DOX, *NEAT1* expression was -155.42-fold and -69.55-fold in MCF-7 and MDA-MB231 cells, respectively. In contrast, a -7.78-fold decrease was observed in MCF-10A cells (Table 1). Thus, DOX may act through *NEAT1* in BC cell lines.

miR410-3p upregulation in cancer cell lines treated with DOX

miR410-3p in two BC cell lines and normal mammary epithelial cells was detected by RT-PCR after DOX treatment. Doxorubicin treatment increased *miR410-3p* expression while reducing *NEAT1* expression in the cells (Table 1 and Figure 1).

The occurrence of the DOX response for a longer time and at a higher concentration in aggressive cells

In the present study, IC_{50} values were calculated for DOX in the MCF-7 and MDA-MB-231 cell lines. The IC_{50} values of DOX for MCF-7 and MDA-MB231 cell lines were 6.14 and 1.28 µM at 48 and 72 h, respectively (Figure 2 and 3). In the MCF-10A control cell line, the IC_{50} value was 8.3 µM at 24 h after DOX treatment (Figure 4).

NEAT1 Targets and Signaling Pathway Analysis

The potential targets of lncRNA *NEAT1* were identified utilizing the Encori tool. The targets were hierarchically classified employing the ShinyGO software, and Chart analyses were conducted. The results indicated an association between the identified targets and breast cancer-associated genes (Figure 5A). Furthermore, the function sets and signaling pathways of potential targets were analyzed with PantherDB. The analysis yielded evidence that *NEAT1*, as a long non-coding RNA (lncRNA), plays critical roles in various biological processes, particularly cell proliferation, apoptosis, stress response, and RNA processing. The biological process analyses (GO terms) presented in the figures support *NEAT1*'s involvement in these mechanisms (5B). This figure provides a comprehensive overview of diverse biological processes and their connections to genes. Processes such as DNA damage response and cellular response to stimulus may suggest that *NEAT1* contributes to tumor growth by enhancing tolerance to genetic damage in cancer cells. Figure 5C shows that demonstrates that *NEAT1* plays a significant role in general categories such as biological regulation and cellular processes. Additionally, *NEAT1*'s involvement in cell death indicates its potential to suppress apoptosis, thereby facilitating the survival of tumor cells (5C).

Table 1. *NEAT1* and *Mir410-3p* Expression Fold Changes in Cancer Cell Lines

	MCF-7	MDA-MB231	MCF-10A
NEAT-1	-155.42	-69.55	-7.78
p value	0.000016	0	0
miR410-3p	1.21	1.83	1.4
p value	0.006058	0.00003	0

A p-value <0.05 was considered statistically significant

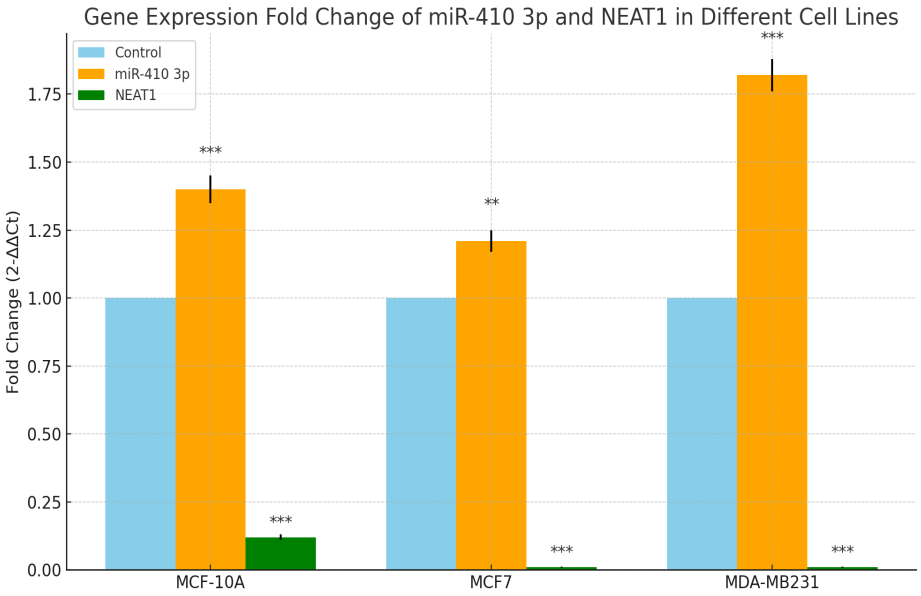

Figure 1. Relative Gene Expression Levels of *miR-410-3p* and *NEAT1* in MCF-7, MDA-MB-231, and MCF-10A cell lines (**p < 0.001, ***p < 0.0001)

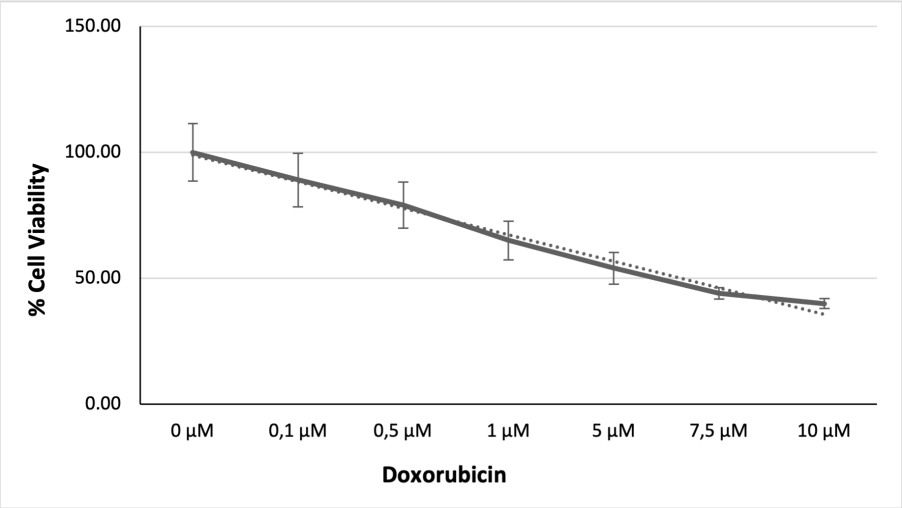

Figure 2. MCF-7 IC_{50} Graph. IC_{50} Values of Cell Lines for Doxorubicin Treatment. Note. IC_{50}, Half-maximal inhibitory concentration.

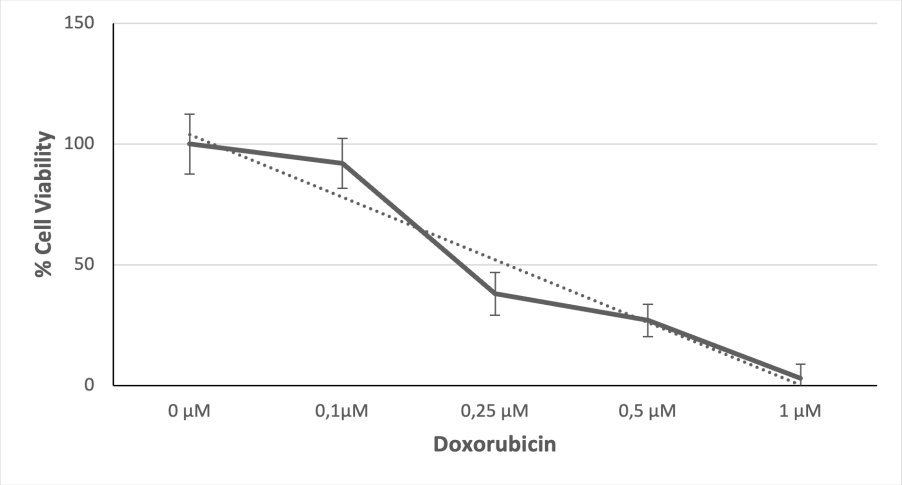

Figure 3. MDA-MB-231 IC_{50} Graph. IC_{50} Values of Cell Lines for Doxorubicin Treatment. Note. IC_{50}, Half-maximal inhibitory concentration.

Discussion

In the genome, lncRNAs play diverse roles in post-transcriptional pathways, gene regulation, and epigenetic interactions that contribute to tumorigenesis. In many cancers, lncRNAs have oncogenic and tumor-suppressive

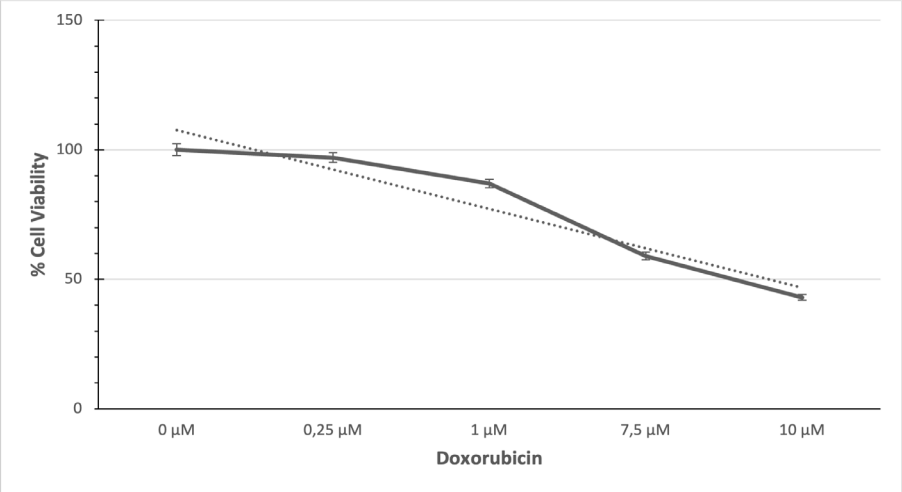

Figure 4. MCF-10A IC_{50} Graph. IC_{50} Values of Cell Lines for Doxorubicin Treatment. Note. IC_{50}, Half-maximal inhibitory concentration.

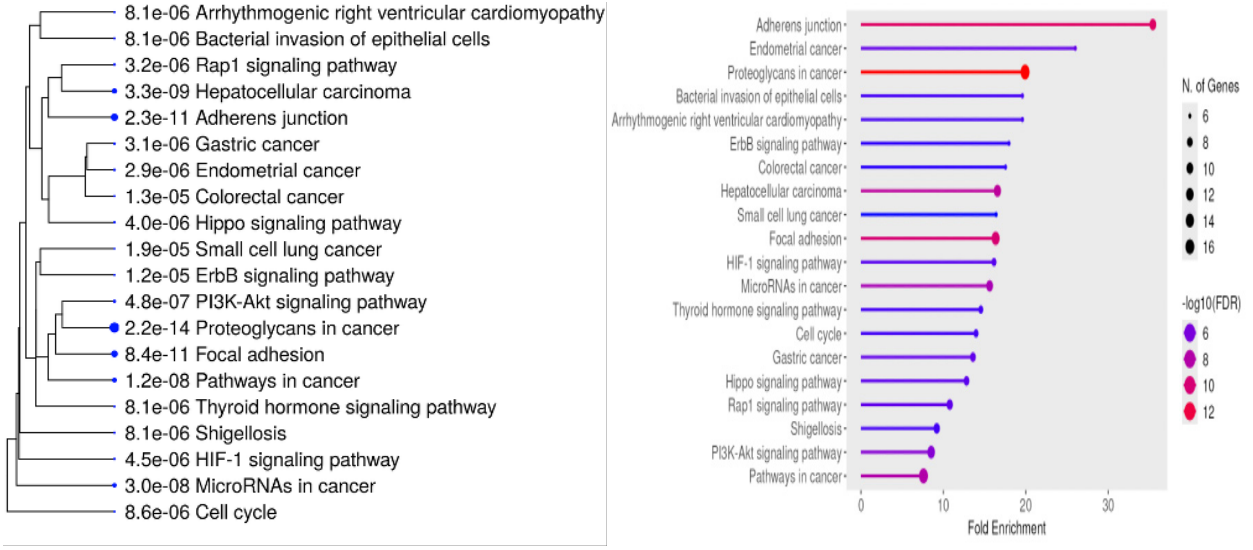

Figure. 5A. Hierarchical Classification and Chart Analysis of NEAT1 Targets

roles. The abnormal expression of lncRNAs may contribute to cancer development [15]. NEAT-1 was detected in the expression sequence experiments in parallel with metastasis-associated MALAT1. An enriched lncRNA in the nucleus is localized within the paraspeckles and is necessary for maintaining their integrity [16,17]. Meta-analyses research demonstrated that *NEAT1* was upregulated in different types of cancer, leading to an unfavorable prognosis and overall poor survival. The first evidence was discovered in recent studies, implying that *NEAT1* plays a vital role in BC biology and that *NEAT1* is a direct target of HIF-2. HIF-2 transcriptionally regulates *NEAT1* expression in BC, *NEAT1* high expression was related to poor overall survival in patients with ER+ BC

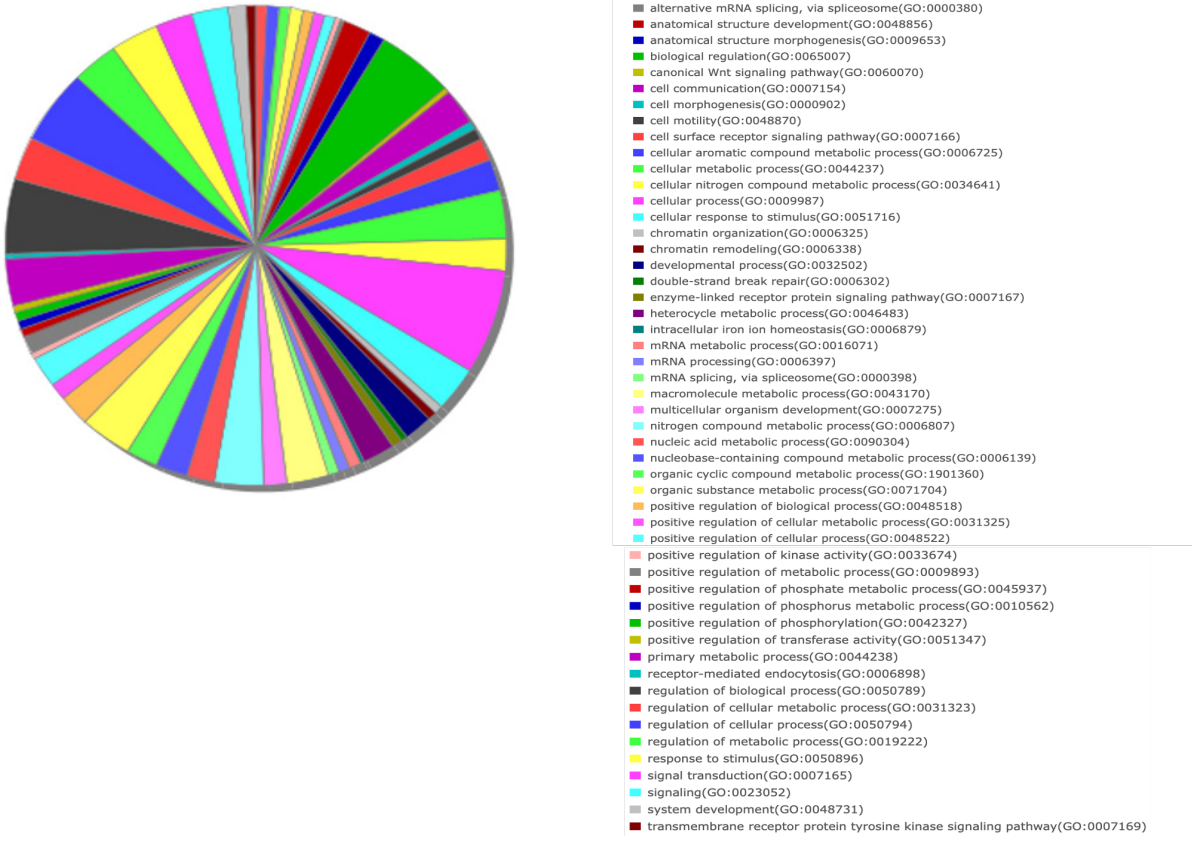

Figure 5B). Gene Ontology (GO) Biological Process Chart of All Genes

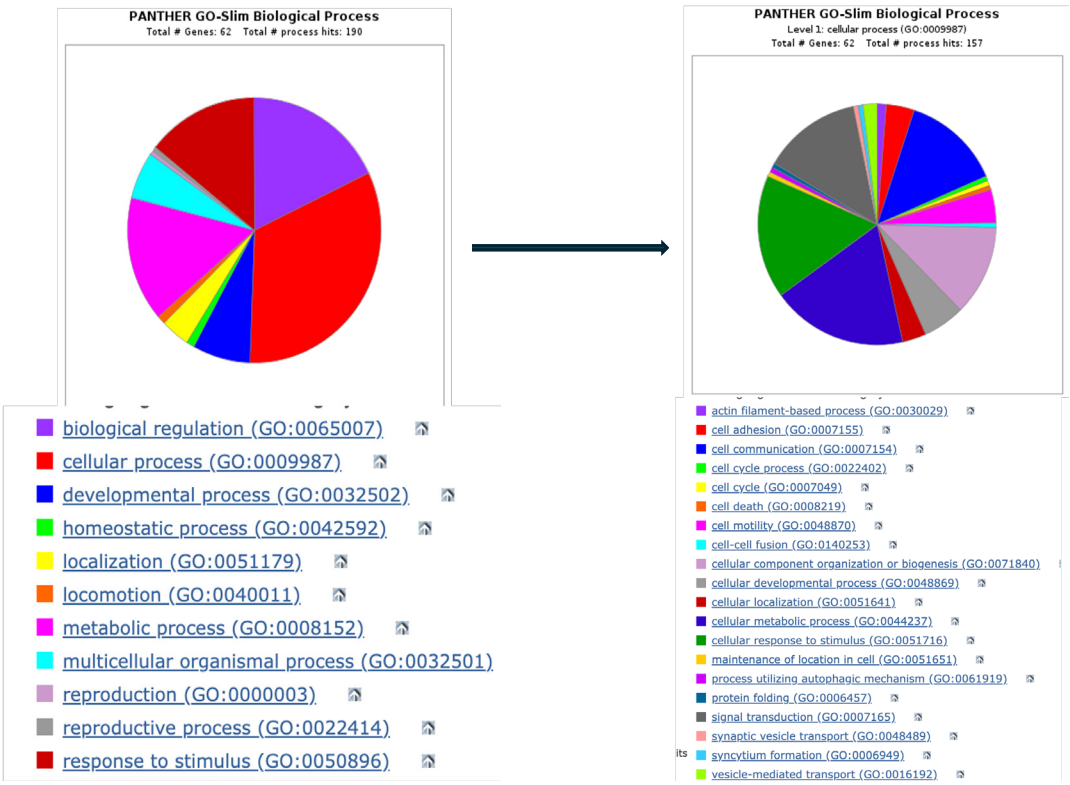

Figure 5C. Cellular Process GO:0009987, 62 associated Genes

[17].

Further, FOXN3 interaction with *NEAT1*/SIN3A represses GATA3 in BC metastasis [18]. In recent years, *NEAT1* has been extensively studied for its contribution to BC progression, and some studies have reported its interaction with a wide range of miRNAs. For instance, the overexpression of miR-548 causes *NEAT1* expression to decrease, finally leading to apoptosis [19]. The BRCA1/*NEAT1*/miR-129-5p signaling axis was also observed to play a role in BC tumorigenesis [20]. Similarly, upregulation of *NEAT1* expression could increase BC cell growth by targeting miR-101. Moreover, *NEAT1* has been implicated in the invasion, cell migration, and regulation of miR-488 and ZEB125 [21]. *NEAT1* competes with different RNAs in the four types of BC and consequently exerts a variety of regulatory functions [22].

The chemotherapeutic drug DOX is well known for its ability to suppress cancer cell proliferation, inhibit topoisomerase II activity, and induce apoptosis. Mitosis and cell cycle progression are limited by DOX activity [23]. Liu et al. reported that the regulation of *NEAT1* and Cyclin D1 (CCND1) in BC is related to the regulation of *miR410-3p*. CCND1 and *NEAT1* were upregulated in BC tissues, whereas *miR410-3p* was downregulated. Higher *NEAT1* expression levels are associated with a lower BC survival rate. In addition, *NEAT1* regulates CCND1 expression in BC cells by sponge *miR410-3p*. Knockdown of *NEAT1* blocked tumor growth in vivo [24]. In our recent study [25], we investigated the role of the *NEAT1*/*miR410-3p* axis in breast cancer cell invasion. Our findings revealed that *NEAT1*, plays a key role in breast cancer cell proliferation and survival. Specifically, we observed that *NEAT1* functions as a molecular sponge for mi 410-3p, thereby modulating its availability and activity. This interaction between *NEAT1* and *miR410-3p* significantly influences the invasive capabilities of breast cancer cells, suggesting that targeting the *NEAT1*/*miR410-3p* axis could be a potential therapeutic strategy for inhibiting breast cancer progression.

NEAT1 knockdown impaired homologous recombination capacity and enhanced Olaparib-induced DNA damage in serous ovarian cancer cells, thereby increasing their sensitivity to Olaparib and offering a significant therapeutic advantage [26]. Our target analysis provided evidence that, *NEAT1* is associated with DNA damage response and DNA repair in cancer cells.

Our gene ontology analysis of potential *NEAT1* targets revealed associations with apoptosis, cell cycle regulation, and cell death. Shin et al. [11], reported that *NEAT1* was found to be overexpressed in the circulation of breast cancer, particularly in TNBC. Its tumor-promoting effects were attributed to dysregulated apoptosis and cell cycle control.

In conclusion, based on our data analysis, DOX plays a role in the regulation of *NEAT1* and *miR410-3p*. Our findings revealed that following doxorubicin treatment, *miR410-3p* levels increased, while *NEAT1* expression was markedly reduced, suggesting that *NEAT1* functions as a molecular sponge for miR-410. These findings indicate that the downregulation of *NEAT1* leads to the upregulation of its target, *miR410-3p*, highlighting its potential as a therapeutic target. Therefore, further investigation is needed to clarify the relationship between *NEAT1* and *miR410-3p*.

Author Contribution Statement

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Ibrahim Acikbas], [Buket Er Urganci], [Zahra Azizi] and [Cihangir Dogan]. Bioinformatics analyses, graphics, and contributed to writing of the discussion by [Pervin Elvan Tokgun]. The first draft of the manuscript was written by [Zahra Azizi] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare no conflict of interests.

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